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| EXAMINER | |
|---|---|
| HAMA, JOANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/824,632 | KUMAR ET AL. | |
| | Examiner | Art Unit | |
| | Joanne Hama, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant filed a response to the First Action on the Merits July 14, 2005. Claims 2 and 8 are cancelled. Claims 1 and 3-7 are amended.

Claims 1 and 3-7 are under examination.

### ***Withdrawn Rejections***

***35 U.S.C. § 103(a)***

Applicant's arguments, see pages 5-6 of Applicant's response, filed July 14, 2005, with respect to the rejection of claims 1, 3-7 have been fully considered and are persuasive. Applicant has pointed out that there is no indication that increase in cardiomyocyte size decreases blood vessel diameter. The Examiner agrees with this assertion. The rejection of claims 1-7 has been withdrawn.

### ***New Rejections***

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-7 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a transgenic, homozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of its genome, wherein the mouse exhibits blood pressure

that is higher than a mouse that does not have a disruption in IEX-1 in its genome and expresses no IEX-1 protein, and

a transgenic, heterozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of the genome, wherein breeding said transgenic heterozygous mice result in a transgenic, homozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of its genome, wherein the homozygous mouse exhibits blood pressure that is higher than a mouse that does not have a disruption in IEX-1 in its genome, and expresses no IEX-1 protein,

does not reasonably provide enablement for

a mouse heterozygous for a disrupted IEX-1 sequence, wherein a mouse homozygous for said disrupted IEX-1 sequence has a level of blood pressure that is higher than the level observed in a control mouse not homozygous for said disrupted IEX-1 sequence and lacks expression of an IEX-1 polypeptide.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record, April 11, 2005.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to

make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Applicant's arguments, see pages 4-5 of Applicant's response, filed July 14, 2005, with respect to the rejection of claims 1, 3-7 have been fully considered. Regarding the issue of scope of "non-human mammal," Applicant has amended the claims and narrowed the scope from "non-human mammal" to "mouse." With regards to Applicant narrowing the scope of the claimed invention, the rejection of claims 1 and 3 are withdrawn. However, claims 4-6 encompass mammals and remain rejected.

Applicant has not addressed other issues of rejection as discussed by the Examiner in the First Office Action, April 11, 2005.

On page 5, 3rd parag. to page 7 of the First Office Action, April 11, 2005, the Examiner pointed out that the claims encompassed transgenic mice comprised of an exogenous expression construct comprising a promoter, operatively linked to a nucleic acid sequence encoding any species of IEX-1, wherein the nucleic acid sequence encoding IEX-1 comprises a disruption. The Examiner pointed out that the art teaches

that making transgenic animals is unpredictable. While the specification teaches how to make and use IEX-1 -/- null mice, wherein exons 1 and 2 and intron 1 of the IEX-1 gene in the mouse's genome is disrupted (specification, page 8), the specification does not teach how to make a mouse comprising a transgene construct comprising a truncated IEX-1 sequence. Nothing in the specification or the art provides guidance as to what truncations of IEX-1 to make, what tissues to express the truncated construct, and that the mice comprising these constructs has a higher level of blood pressure than a wild type mouse. Applicant has not provided any guidance to the contrary, and thus, the rejection regarding this issue stands.

Upon further consideration, additional rejections under U.S.C. § 112, 1st parag. are addressed as follows.

Claim 7 is drawn to a mouse that comprises a heterozygous disruption of IEX-1. In addition to encompassing heterozygous mice whose somatic and germ cells comprise the disruption, the claim encompasses heterozygous mice that are mosaic. Nothing in the specification teaches that mosaic heterozygous mice comprising a disruption of IEX-1 have any phenotype. Further, nothing in the art or the specification teaches that a heterozygous mosaic mouse, wherein the heterozygous disruption of IEX-1 is only in somatic cells can be used to generate homozygous IEX-1 disrupted mice. Thus, while a heterozygous mouse comprising in its somatic and germ cells, a disruption of IEX-1 in its genome, wherein the heterozygous mouse is used to generate a homozygous mouse comprising in its somatic and germ cells, a disruption of IEX-1 in its genome, wherein the homozygous mouse lacks expression of an IEX-1 polypeptide

and exhibits a blood pressure that is higher than the level observed in a control mouse not homozygous for the disruption of IEX-1 in its genome, is enabled, the embodiment wherein the mouse is mosaic is not enabled.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-6 recite the limitation "wherein said mammal" in claim 1. There is insufficient antecedent basis for this limitation in the claim. There is no “mammal” in claim 1.

Claim 7 uses the phrase, “and lacks expression of an IEX-1 polypeptide.” This phrase is unclear because it is not clear whether the phrase refers to the control mouse or to the homozygous IEX-1 disrupted mouse.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3-7 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Lehoux and Tedgui (2003, Circulation Research, 93: 1139-1141, see IDS) in view of Capecchi (1989, Trends in Genetics, 5: 70-76, previously cited on 892 of April 11, 2005).

Lehoux and Tedgui teach that work by Schulze et al. show a biological relationship between *iex-1* and inhibition of proliferation of smooth muscle cells (SMCs). In their work, Schulze et al. teach that 1) *iex-1* is induced in human aortic SMCs exposed to cyclic stretch or to several growth factors, 2) stretch-induced *iex-1* expression is regulated by NF-κB, and 3) overexpression of *iex-1* inhibits proliferation of SMCs in culture and modulates intimal hyperplasia induced by vascular injury in vivo (Lehoux and Tedgui, page 1139, 2nd col., 3rd parag.). Lehoux and Tedgui also teach that work by Wu and Standley et al demonstrate that, "given that growth factor secretion and growth factor receptor activation are stimulated by cyclic stretch in SMCs, contributing to cell proliferation, it is conceivable that the mitogenic pathways fueled by growth factors accumulating over 48 hours of cell culture eventually reach a threshold beyond which they overcome antiproliferative effects of endogenous *iex-1* (Lehoux and Tedgui, page 1140, 1st col., 2nd parag.). Lehoux and Tedgui teach that work by Yamasaki et al. demonstrated that *iex-1* overexpression effectively abated intimal hyperplasia, but the role for NF-κB-dependent *iex-1* expression in this context is obscure because intimal hyperplasia can just as well be prevented using NF-κB decoy

strategies, which would block *iex-1* transcription (Lehoux and Tedgui page 1140, 1st col., 2nd parag. to 2nd col., 1st parag.). Lehoux and Tedgui teach that Schulze et al. point out that the strain-dependent expression of *iex-1* may represent a mechanically induced modulation of SMCs in culture leading toward a more physiological phenotype. While *iex-1* was found to be constitutively expressed in native, non-injured vessels, it was barely detectable in intimal hyperplasic lesions produced by balloon injury (Lehoux and Tedgui, page 1140, 2nd col., 2nd parag.). Lehoux and Tedgui teach that their results demonstrate that NF-κB inhibition induces apoptosis not only in vessels maintained in organ culture at elevated transmural pressure, but even in vessels cultured at physiological pressure (Lehoux and Tedgui page 1140, 2nd col., 2nd parag.). Taken together, the results demonstrate that there is fundamental role for NF-κB in the vessel, preventing cell proliferation through *iex-1* transcription under physiological mechanical stimulation while maintaining SMC survival both in physiological conditions and in conditions or exaggerated vessel stretch, via antiapoptotic gene expression (Lehoux and Tedgui, page 1140, 2nd col., 2nd parag., see also Figure on page 1140). Lehoux and Tedgui teach that further research is necessary to extend these initial observations and ascertain the functional roles of *iex-1* in vascular biology. Loss-of-function experiments will be particularly useful to provide direct evidence for a role of *iex-1* in SMC proliferation under physiological or pathological conditions (Lehoux and Tedgui, page 1140, 2nd col., 3rd parag.).

While Lehoux and Tedgui teach the biological role of *iex-1* in SMCs and point out that loss-of-function experiments will be particularly useful to provide direct evidence for

a role of *iex-1* in SMC proliferation, they do not teach how to make a transgenic mouse comprising a disruption in *iex-1*.

Capecchi teaches how to generate a transgenic mouse comprising an alteration in its genome, wherein the alteration is designed specifically to an artisan's specifications. Capecchi teaches that "through gene targeting, the potential now exists to generate mice of any desired genotype. The experimenter chooses both which gene to mutate and how to mutate it. The criteria for selecting which gene to mutate can be based on knowledge generated within the species or from other species. The ability to choose how to mutate the gene will permit a thorough analysis of the function of any cloned gene through the generation of multiple mutant alleles. Not only can gene targeting be used to generate null alleles, it can be used to modify any property of the gene that affects its function, such as its transcriptional pattern, its mRNA or protein maturation pattern, or the ability of its protein product to interact with other gene products (Capecchi, page 70, 1st col, 3rd parag.)." Capecchi teaches that ES cells are obtained from mouse blastocysts. When ES cells are reintroduced into a blastocyst, they contribute efficiently to the formation of all tissues in a chimeric mouse, including the germ line. Further, Capecchi teaches that when ES cells are manipulated in vitro, they do not lose their capacity to generate germ-line chimeras (Capecchi, page 72, under "ES cells"). Capecchi also teaches that parameters used to obtain the targeting construct and to increase the chances of foreign DNA integration into a specific site. Capecchi teaches that "the frequency of recombination between co-introduced DNA molecules is roughly proportional to the extent of homology between them." With

regards to increasing one's chances that the targeting construct undergoes recombination, Capecchi teaches that there is a peak of activity in the S phase of the cell cycle (Capecchi, pages 70-71, under "Homologous Recombination in Cultured Mammalian Cells"). Capecchi also teach how to select for specific recombination events using "Positive-Negative Selection." In this method, the vector is designed such it comprises 10-15 kb of DNA homologous to the target gene X, a $neo^r$ gene inserted into an exon of that sequence, and an HSV-tk gene adjacent to the sequence. The vector is designed such that when the endogenous X sequence is replace by the exogeous DNA via homologous recombination, the HSV-tk gene will not be transferred into the target gene. Exclusion of the HSV-tk gene during homologous recombination occurs because the HSV-tk gene represents a discontinuity in the incoming vector between homology and nonhomology with the endogenous target sequence (Capecchi, page 74, 2nd col. under "Positive-Negative Selection (PNS)"). Capecchi teaches targeted disruptions of gene would not only reveal the phenotypes associated with inactivation of the individual genes, but would also define the epistasis of genes in a network (Capecchi, page 75, 2nd parag. under "Uses of Gene Targeting").

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make a transgenic mouse comprising a targeted disruption in the *iex-1* gene.

One having ordinary skill in the art would have been motivated to make a mouse comprising a disruption in *iex-1*, in order to obtain a mouse comprising a phenotype

associated with disruption of *iex-1* and epistatic information as to what the relationship is between *iex-1*, stretch, growth factors, anti-apoptosis, and proliferation.

There would have been a reasonable expectation of success given the teachings of Lehoux and Tedgui for demonstrating that IEX-1 has a role in controlling apoptosis and cell proliferation in SMCs upon stimulation with stretch or with growth factors and given the teachings of Capecchi who point out the elements used to generate mice comprising a targeted disruption in a gene of interest.

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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